REMARKS

Claims 8-11, 16-18, 25-28 and 35 currently appear in this application. The Office Action of February 11, 2008, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Claim Objections

Claim 19 is objected to because of the term, "the" is misspelled.

As claim 19 has now been cancelled, this objection is moot.

Rejections under 35 U.S.C. 112

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

As claims 19 and 20 have now been cancelled, this rejection is now moot.

Art Rejections

Claims 8-11 and 19-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miura et al., US 5,959,088 in view of Mirza et al., *AAPS Pharm. Soc.*, 20903, **5(2)** and Spanton et al., US 5,945,405.

This rejection is respectfully traversed. It is respectfully submitted that Mirza is not a reference against the present application because Mirza was published April 14, 2003, and the present application has a priority date of January 14, 2003. Accordingly, Mirza cannot be relied upon as prior art t o deny the

For the foregoing reason, it would not have been prima facie obvious to one skilled in the art to prepare Crystal Forms G and to prepare a hydrate Crystal Form D from Crystal Forms G by combining Mirza with the other cited references, since Mirza cannot be used as a reference,

Claims 16-18, 23, 25, 27, 29, 31 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miura et al,. in view of Mirza and Spanton as applied above, and further in view of Bosch et al., US 6,504,017.

This rejection is respectfully traversed, As with the previous rejection, this rejection relies upon Mirza, which was published after the priority date of the subject application Accordingly, **Mirza cannot be prior art** because of the later filing date. Please note that claims 16-18, 23, 25, 276, 29, 31 and 33 have been cancelled, so this rejection is moot with respect to those claims.

The Crystal Forms G, namely, Crystal Form G1, Crystal Form G2 and Crystal Form G3 are crystal forms which have specific X-ray diffraction patterns at 5.4`, 10.4`m 10.7` and 12.1`. These crystal forms are quite different from Crystal Forms A, C and D. Therefore, it can be said that claims 8-11 are novel over each of the references cited by the Examiner. In addition, these new crystal forms are useful as intermediates to obtain Crystal Form D hydrates. Therefore, claims 8-11 are not anticipated by or obvious over the cited references.

With respect to claims 27 and 28, it should be appreciated that claim 27 relates to a process for preparing Crystal Form D of a hemifumarate of a compound of formula (I) via Crystal Form F, and for preparing Crystal form D anhydrate from Crystal Form E **and not via an acetone, nethylethylketone or tetrahydrofuran solvent.** Claim 28 relates to Crystal Form D hydrate which is obtained by the process of claim 27.

Claim 27 is drawn to a process for preparing Crystal Form D hydrate via Crystal Form F and Crystal form D anhydrate from Crystal Form E. The process of claim 27 differs from that of Miura in that while the process of claim

27 advanced **via Crystal Form E**, the Miura process does not. This, claims 27 and 28 are patentably distinct from the disclosure of Miura and Bosch. By preparing Crystal Form D hydrate via Crystal Form E, Crystal Form D is obtained that is particularly well suited for making pharmaceuticals, particularly in tabletting the compound because of its larger particle size and less residual solvent. These advantageous effects are described in the specification of US Patent Application 10/399,146. Copies of pages 15 and 16 of this application are submitted herewith. The Table on page 16 of this application shows the properties of the D-type crystals prepared via E-type crystals (Examples 2 to 8) and prior art D-type crystals (Comparison Examples 1 and 2). Also enclosed is a copy of page 18 from the '146 application, which describes the D Form Crystals prepared by the method claims in claim 27 as having superior properties, including a reduced content of residual solvent and high stability for formulation. Accordingly, it is respectfully submitted that the process of claim 27 and the crystal claimed in claim 28 formed by this process is not obvious over Miura even in view of Bosch.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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[Comparison Example 1]

A fumarate salt of compound (I) (10.8 kg) was dissolved at 25°C in a mixed solvent of ethyl acetate (87.6 kg) and methanol (8.5 kg). After the solution was concentrated, ethyl acetate (80.8 kg) was added at 25°C to the concentrated residue, followed by stirring at 25°C for 1 hour to give a C-form crystal. After addition of water (1.5%, 1.3 kg), this C-form crystal was cooled to 15°C and stirred for 1 hour to ensure its conversion into D-form crystal. The suspension was further cooled to -10°C and stirred for 1 hour. The resulting crystal was then centrifuged to give a wet D-form crystal (12.7 kg). This wet D-form crystal was dried under reduced pressure at 60°C for 16 hours to give the D-form crystal of the fumarate salt of compound (I) (10.8 kg, yield 87.4%, average particle size: 82 μm). Tabletting troubles were observed in this D-form crystal when used as a main component to prepare tablets.

A C-form crystal of a fumarate salt of compound (I) was similarly treated in accordance with Comparison Example 1 to give a D-form crystal without going via an E-form crystal (Comparison Example 2).

Table 1 summarizes the properties of the D-type crystals prepared via E-type crystals (Examples 2 to 8) and the prior art D-type crystals (Comparison Examples 1 and 2).

Table 1

	Percentage of water (%)	Prepared via E-type crystal	Conditions for conversion of E-type crystal into D-type crystal	Drying conditions	Content of residual solvent (ppm)	Particle size (μm)	Tabletting trouble
Example 2	2.4	Completely	15°C, 3hr → -10°C	Reduced pressure 60°C, 8hr	78	302	---
Example 3	2.6	Completely	15°C, 6hr → -10°C	Reduced pressure 60°C, 8hr	---	197	---
Example 4	2.0	Partially	15°C, 1hr → -10°C	Reduced pressure 60°C, 28hr	988	141	No
Example 5	2.0	Partially	15°C, 1hr → -10°C	Reduced pressure 60°C, 10hr	845	197	No
Example 6	2.0	Partially	13°C, 0.5hr → -10°C	Reduced pressure 60°C, 9hr	1049	---	---
Example 7	2.0	Partially	15°C, 1hr → -10°C	Reduced pressure 60°C, 6hr	647	163	No
Example 8	2.0	Partially	15°C, 1hr → -10°C	Reduced pressure 60°C, 10hr	893	185	No
Comparison Example 1	1.5	Not	---	Reduced pressure 60°C, 16hr	2228	82	Yes
Comparison Example 2	1.5	Not	---	Aeration 45°C, 20hr	1610	61	Yes

INDUSTRIAL APPLICABILITY

The E-form crystal of a fumarate salt of compound (I) according to the present invention enables the preparation of the D-form crystal with superior properties including a reduced content of residual solvent and high suitability for formulation. More specifically, the E-form crystal is characterized by (1) providing pharmaceuticals with superior quality and (2) allowing the efficient preparation of pharmaceuticals; it is therefore extremely useful in pharmaceutical preparation.